

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number  
**WO 2004/022033 A1**

(51) International Patent Classification<sup>7</sup>: A61K 9/00, 38/29

(21) International Application Number:  
PCT/US2003/027770

(22) International Filing Date:  
4 September 2003 (04.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/408,165 4 September 2002 (04.09.2002) US

(71) Applicant: MICROCHIPS, INC. [US/US]; 6-B Preston Court, Bedford, MA 01730 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors: AUSIELLO, Dennis; 38 Bradford Road, Wellesley Hill, MA 02481 (US). SANTINI, John, T., Jr.; 12 Maynard Circle, North Chelmsford, MA 01863 (US). HERMAN, Stephen, J.; 50 Sunset Rock Road, Andover, MA 01810 (US). PRESCOTT, James, H.; 85 Trowbridge Street, #3, Cambridge, MA 02138 (US).

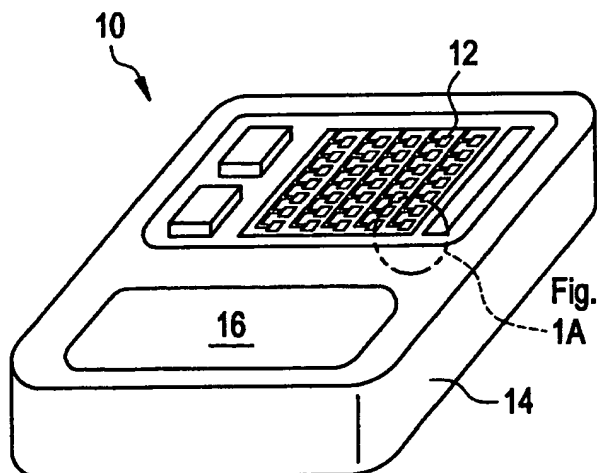
**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(74) Agents: KING, Kevin, W. et al.; Sutherland Asbill & Brennan LLP, 999 Peachtree Street, N.E., Atlanta, GA 30309-3996 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND DEVICE FOR THE CONTROLLED DELIVERY OF PARATHYROID HORMONE



(57) Abstract: Method and devices are provided for extended and controlled delivery of parathyroid hormone to a patient. The method includes implanting a medical device into the patient, the medical device comprising a substrate, a plurality of reservoirs in the substrate, a release system contained in each of the reservoirs, wherein the release system comprises parathyroid hormone; and controllably releasing a pharmaceutically effective amount of the parathyroid hormone from the reservoirs. The parathyroid hormone can be released intermittently, such as once daily over an extended period (e.g., two months, ten months, or more.). The device can further include reservoirs containing a bone resorption inhibitor or other drug for release. The devices are useful in delivering PTH for the treatment and prevention of bone loss, such as associated with osteoporosis.

WO 2004/022033 A1

BEST AVAILABLE COPY

## METHOD AND DEVICE FOR THE CONTROLLED DELIVERY OF PARATHYROID HORMONE

### Background of the Invention

5           This invention is generally in the field of methods and devices for the controlled delivery of parathyroid hormone (PTH) to patients, for example, to promote the growth and maintenance of bone tissue.

          The mechanism of bone loss is not completely understood, but the disorder effectively arises from an imbalance in the formation of new healthy bone and the  
10   resorption of old bone. The bone loss includes a decrease in both mineral content and protein matrix components of the bone, and leads to an increased rate of bone fracture. These fractures, predominantly femoral bones and bones in the forearm and vertebrae, lead to an increase in general morbidity and a loss of stature and mobility, as well as an increase, in many cases, in mortality caused by complications from the  
15   fracture.

          Bone loss occurs, for example, in post-menopausal women, patients who have undergone hysterectomy, patients undergoing or who have undergone long-term administration of corticosteroids, patients suffering from Cushing's syndrome, and patients having gonadal dysgenesis. Unchecked bone loss can lead to osteoporosis, a  
20   major debilitating disease whose prominent feature is the loss of bone mass (decreased density and enlargement of bone spaces) without a reduction in bone volume, producing porosity and fragility. Post-menopausal osteoporosis is associated with the large and rapid loss of bone mass due to the cessation of estrogen production by the ovaries. One source reports that ten million individuals in the United States are  
25   estimated to already have osteoporosis and almost 34 million more are estimated to have low bone mass, placing them at increased risk for the disease, and that one out of two women and one in eight men over age 50 will have an osteoporosis-related fracture in their lifetime.

          PTH is involved in calcium and skeletal homeostasis. It stimulates the tubular  
30   resorption of calcium by the kidney and inhibits the reabsorption of phosphate and bicarbonate by the proximal renal tubules. PTH also affects the kidney by stimulating production of a vitamin D metabolite (1,25(OH)<sub>2</sub>D), which is an *in vivo* stimulator of osteoclasts and an enhancer of intestinal calcium absorption. The increase in intestinal calcium absorption following PTH stimulation is mediated by this vitamin

D metabolite. *In vivo*, PTH stimulates osteoclastic bone resorption with the release of calcium into the circulation, and causes proliferation of osteoblasts.

With the general understanding of bone growth and its regulation, various approaches have been proposed to treat diseases involving reduction of bone mass and accompanying disorders by the administration of bone resorption inhibitors and/or anabolic agents, such as PTH. Examples of such approaches include U.S. Patent No. 6,239,144 to Galvin et al., which discloses treating conditions associated with a lack of PTH by administering a compound having activity as a tachykinin receptor antagonist, which reportedly can increase the secretion of PTH; U.S. Patent No. 5,670,514 to Audia et al., which discloses inhibiting bone loss by the administration of a 5 $\alpha$ -reductase inhibitor (a benzoquinolin-3-one), alone or in combination with another bone anabolic agent, such as PTH; and U.S. Patent No. 5,510,370 to Hock, which discloses treatment of bone loss in a patient by administering PTH sequentially, concurrently, or simultaneously with raloxifene.

It has been established that low dose, intermittent administration of PTH is associated with anabolic effects in humans, whereas higher dose, continuous administration of PTH is associated with catabolic effects. Rubin & Bilezikian, *Int. J. Fertil.* 47(3):103-15 (2002); Schaefer, *Novartis Found Symp* 227:225-39 (2000). U.S. Patent No. 6,239,144 discloses that there is a dose dependent stimulation of the mineral apposition rate by PTH and that the result of the administration of PTH on skeletal homeostasis depends on how the hormone is administered. For the same daily dose, the bone volume shows a dose dependent increase if the daily dose of the hormone is given as one single injection. However, when the same daily dose is administered by continuous infusion with a subcutaneous mini-osmotic pump, the result is bone loss. Intermittent injection causes practically no effect on the serum calcium levels, whereas infusion causes a dose dependent increase in the serum calcium. The effects of PTH administered by these two routes on bone mineral apposition rate appeared to be the same. Once-daily injections are an undesirable means for the treatment and prevention of bone loss, because treatment and/or prophylaxis must occur over an extended period and frequent injections would be objectionable and would discourage patient compliance with the treatment. It would thus be desirable to provide alternative means for administering PTH intermittently, alone or in combination with other drugs useful in promoting bone growth and/or

inhibiting bone loss.

There are myriad technologies generally referred to as providing controlled or sustained drug delivery, which deliver drug by a variety of routes. Although some controlled release methods and devices have been somewhat effective in controlling protein or peptide delivery in the body, several limitations can influence their suitability or practicality for administering a particular therapeutic agent, such as PTH. For example, many "controlled" release drug delivery systems may not provide a well-defined release profile. Other technologies may be suitable for continuous release (e.g., an ALZET<sup>TM</sup> osmotic pump), but not pulsatile release. Yet other technologies that are suitable for delivery of small molecule drugs would be unsuitable for long-term storage and delivery of fragile protein or peptide drug molecules. Such molecules may, for example, undergo degradation and denaturation associated with exposure to moisture, elevated temperatures (e.g., 37 °C), and/or by other means. Still other drug delivery systems undesirably would require periodic (frequent) replacement or refilling, or an unacceptably large size in order to provide for the administration of drug for long-term therapy.

It therefore would be desirable to provide a drug delivery system capable of accurately delivering a therapeutically and/or prophylactically effective amount of PTH, alone or in combination with other drugs. It desirably would provide well-defined pulsatile release of PTH over an extended period of time in a small, anatomically acceptable configuration, without requiring refilling of the delivery device with drug, repeated injections, or repeated replacement of part or the entire device over the course of treatment. In addition, it would be desirable for the drug delivery rate to be adjustable over the course of treatment.

#### **Summary of the Invention**

Method and devices are provided for extended and controlled delivery of parathyroid hormone to a patient, for example, for the treatment and prevention of bone loss, such as associated with osteoporosis.

In one aspect, the method includes implanting a medical device into the patient, the medical device comprising a substrate, a plurality of reservoirs in the substrate, a release system contained in each of the reservoirs, wherein the release system comprises parathyroid hormone; and controllably releasing a pharmaceutically effective amount of the parathyroid hormone from the reservoirs.

In one embodiment of the method, the step of controllably releasing provides intermittent release of the parathyroid hormone. In one embodiment, the parathyroid hormone is released in a pulsatile manner, each pulse having a duration of less than four hours.

5 In one embodiment of the method, the parathyroid hormone is released daily in intermittent doses of between about 10 and 300  $\mu$ g. In one embodiment, the daily intermittent doses are released over a period of ten months or more.

In one embodiment of the method, the pharmaceutically effective amount of the parathyroid hormone, released over a first period of time, is effective to form bone  
10 tissue. In another embodiment, the method further includes releasing a pharmaceutically effective amount of a bone resorption inhibitor, released over a second period of time, to maintain bone tissue at a level present after the first period of time. In one embodiment, the bone resorption inhibitor is selected from the group consisting of bisphosphonates, selective estrogen receptor modulators, calcitonins,  
15 vitamin D analogs, and calcium salts.

In another aspect, the implantable device for the extended, controlled delivery of parathyroid hormone to a patient comprises a substrate, a plurality of reservoirs in the substrate, a release system contained in each of the reservoirs, wherein the release system comprises parathyroid hormone, and a control means for selectively releasing  
20 a pharmaceutically effective amount of the parathyroid hormone from each of the reservoirs. In one embodiment, the device releases a pharmaceutically effective amount of parathyroid hormone once daily over a period of at least six months.

In one embodiment, the device further includes at least one reservoir which contains a second release system comprising a drug other than parathyroid hormone.  
25 For example, the drug could be an anti-resorptive agent.

In one embodiment of the device, each of the reservoirs contains between about 10 and 40  $\mu$ g of parathyroid hormone for release.

In one embodiment, the device includes 300 or more reservoirs, each containing a release system comprising parathyroid hormone.

30 In one embodiment of the device, the release system comprises parathyroid hormone in combination with a pharmaceutically acceptable excipient. For example, the release system could include parathyroid hormone suspended in a non-aqueous vehicle. As another example, the PTH could be dried or lyophilized with an excipient

that promotes re-dissolution upon release. Such an excipient could be for example, polyethylene glycol having a molecular weight between about 100 and 10,000 Daltons.

In one embodiment of the device, the control means includes reservoir caps  
5 covering the release system of the reservoirs. In one embodiment, the  
control means further comprises means for actively disintegrating or permeabilizing  
the reservoir caps. In one embodiment, the means for actively disintegrating  
comprises a power source for passing an electric current or potential through the  
reservoir caps. In a specific embodiment, the reservoir caps comprise an electrically  
10 conductive material and are electrically connected to an electrical input lead and to an  
electrical output lead, and the means for actively disintegrating or permeabilizing the  
reservoir cap comprises means for selectively applying an electrical current through  
the reservoir cap, via the input lead and output lead, in an amount effective to locally  
heat the reservoir cap to cause the reservoir cap to disintegrate to permit release of the  
15 parathyroid hormone. In another specific embodiment, the means for actively  
disintegrating the reservoir cap comprises a cathode, a microprocessor, a timer, and a  
demultiplexer, and wherein the reservoir caps each comprise an anode and upon  
application of an electric potential between the cathode and anode the reservoir cap  
disintegrates to permit release of the parathyroid hormone.

20 In one embodiment, the device includes a sensor, such as one that measures  
plasma calcium.

In another embodiment, the control means comprises two or more layers of  
release system having different compositions. Such an embodiment can effectively  
provide a passive control system for effecting pulsatile release.

#### 25 **Brief Description of the Drawings**

Figure 1 is a perspective view of one embodiment of an implantable active-  
release microchip device for delivery of parathyroid hormone.

Figure 2 is a perspective view of another embodiment of an implantable  
active-release microchip device for delivery of parathyroid hormone.

30 Figure 3 is a cross-sectional view of one embodiment of a passive release  
microchip device for delivery of parathyroid hormone.

Figures 4A and 4B are cross-sectional views of two of the many possible  
embodiments of substrate/reservoir geometries: straight walled reservoirs (Figure 4A)  
and combination straight and tapered walled reservoirs (Figure 4B).

Figure 5 is a cross-sectional view of one embodiment of a passive release device substrate having a layered release system for controlling release as well as for controlling aggregation and precipitation of PTH.

Figure 6 is a plan view of one embodiment of the medical device described  
5 herein for intravaginal delivery of PTH.

Figure 7 is a cross-sectional view of the device shown in Figure 6.

### **Detailed Description of the Invention**

Implantable medical devices have been developed for the controlled delivery of parathyroid hormone. The device comprises a substrate comprising a plurality of  
10 reservoirs; a release system comprising parathyroid hormone contained in the reservoirs; and a means for controllably releasing a pharmaceutically effective amount of the parathyroid hormone from the reservoirs.

In one embodiment, the medical device comprises a microchip device. As used herein, a "microchip" is a miniaturized device fabricated using methods  
15 described in U.S. Patents No. 5,797,898 and No. 6,123,861, to Santini, Jr. et al., as well as other methods commonly applied to the manufacture of integrated circuits and MEMS (MicroElectroMechanical Systems) such as ultraviolet (UV) photolithography, reactive ion etching, and electron beam evaporation, as known in the art, as well as MEMS methods that are not standard in making computer  
20 microchips, including those described, for example, in PCT WO 01/41736 and Madou, *Fundamentals of Microfabrication* (CRC Press, 1997), and other micromolding and micromachining and polymer forming techniques known in the art.

As used herein, the terms "comprise," "comprising," "include," and "including" are intended to be open, non-limiting terms, unless the contrary is  
25 expressly indicated.

#### **I. Device Components and Materials**

The device includes a substrate having a plurality of reservoirs, which contain the PTH and, optionally, other drug molecules. The substrate, reservoirs, reservoir caps, control circuitry, and power source are described at least in part herein and/or in  
30 U.S. Patents No. 5,797,898, No. 6,123,861, No. 6,551,838, No. 6,491,666, and No. 6,527,762, as well as U.S. Patent Application Publications No. 2002/0138067, No. 2002/0072784, No. 2002/0151776, and No. 2002/0107470. In one embodiment, control of reservoir cap opening includes electro-thermal ablation techniques, as described in U.S. Patent Application No. 10/641,507, filed August 15, 2003.

### The Substrate and Reservoirs

The substrate is the structural body (e.g., part of a device) in which the reservoirs are formed, e.g., it contains the etched, machined, or molded reservoirs. A reservoir is a well, a container. MEMS methods, micromolding, and micromachining techniques known in the art can be used to fabricate the substrate/reservoirs from a variety of materials. See, for example, U.S. Patent No. 6,123,861 and U.S. Patent Application Publication No. 2002/0107470. Examples of suitable substrate materials include metals, ceramics, semiconductors, and degradable and non-degradable polymers. Biocompatibility of the substrate material typically is preferred for *in vivo* device applications. The substrate, or portions thereof, may be coated, encapsulated, or otherwise contained in a biocompatible material (e.g., poly(ethylene glycol), polytetrafluoroethylene-like materials, inert ceramics, titanium, and the like) before use.

The substrate can be flexible or rigid. In one embodiment, the substrate serves as the support for a microchip device. In one example, the substrate is formed of silicon.

The substrate can have a variety of shapes, or shaped surfaces. It can, for example, have a release side (i.e., an area having reservoir caps) that is planar or curved. The substrate may, for example, be in a shape selected from disks, cylinders, or spheres. In one embodiment, the release side can be shaped to conform to a curved tissue surface or into a body lumen. In another embodiment, the back side (distal the release side) is shaped to conform to an attachment surface.

The substrate may consist of only one material, or may be a composite or multi-laminate material, that is, composed of several layers of the same or different substrate materials that are bonded together.

In one embodiment, the substrate is hermetic, that is impermeable (at least during the time of use of the reservoir device) to the molecules to be delivered and to surrounding gases or fluids (e.g., water, blood, electrolytes or other solutions).

In another embodiment, the substrate is made of a strong material that degrades or dissolves over a defined period of time into biocompatible components. Examples of biocompatible polymers include poly(lactic acid)s, poly(glycolic acid)s, and poly(lactic-*co*-glycolic acid)s, as well as degradable poly(anhydride-*co*-imides).

The substrate thickness can vary depending upon the particular device and application using the activation system described herein. For example, the thickness



of a device may vary from approximately 10  $\mu\text{m}$  to several millimeters (e.g., 500  $\mu\text{m}$ ). Total substrate thickness and reservoir volume can be increased by bonding or attaching wafers or layers of substrate materials together. The device thickness may affect the volume of each reservoir and/or may affect the maximum number of

5 reservoirs that can be incorporated onto a substrate. The size and number of substrates and reservoirs can be selected to accommodate the quantity and volume of reservoir contents needed for a particular application, although other constraints such as manufacturing limitations or total device size limitations (e.g., for implantation into

10 desirably would be small enough to be implanted using minimally invasive procedures. Alternatively, the device would be appropriately sized to be inserted into the vagina for intravaginal administration of PTH.

The substrate includes at least two and preferably tens or hundreds of reservoirs. For example, one reservoir could be provided for each daily dose of PTH

15 required, for example, over a 6-, 8-, 10-, or 12-month course of treatment. The substrate could include, for example, 300 to 400 reservoirs, each containing a release system comprising parathyroid hormone.

In one embodiment, the reservoir has a volume equal to or less than 500  $\mu\text{L}$  (e.g., less than 250  $\mu\text{L}$ , less than 100  $\mu\text{L}$ , less than 50  $\mu\text{L}$ , less than 25  $\mu\text{L}$ , less than

20 10  $\mu\text{L}$ , etc.) and greater than about 1 nL (e.g., greater than 5 nL, greater than 10 nL, greater than about 25 nL, greater than about 50 nL, greater than about 1  $\mu\text{L}$ , etc.).

Two of the many possible embodiments of substrate/reservoir geometries are illustrated in Figures 4A and 4B. The embodiment shown in Figure 4A shows substrate 45 having reservoirs 46a and 46b, which are covered by reservoir caps 47a

25 and 47b, respectively. Reservoirs 46a and 46b have straight, i.e. non-tapered, walls. The embodiment shown in Figure 4B shows a laminate substrate, composed of lower portion 45a and upper portion 45b, which has reservoirs 48a and 48b, which are covered by reservoir caps 47a and 47b, respectively. Reservoirs 48a and 48b have a combination of straight walls in the lower portion 45a of the substrate and tapered

30 walls in the upper portion 45b of the substrate.

#### Drug and Release System

The release system comprises a pharmaceutical formulation of the parathyroid hormone. As used herein, "release system" includes the situations where the PTH

molecules are in pure form (e.g., as a lyophilized powder), in suspension, in solution, or in a matrix formed of biodegradable material or another material which releases incorporated PTH molecules by diffusion or disintegration of the matrix. The release system can, for example, include excipients that modulate the rate of release of PTH.

5                   Parathyroid Hormone

As used herein, the term “parathyroid hormone” or “PTH” includes the complete human hormone (hPTH 1-84); fragments of the hormone responsible for bone growth promotion, such as hPTH 1-34 and hPTH 1-38, and analogs in which the amino acid sequence is modified slightly, yet retain bone growth promotion  
10 properties, such as PTH-RP; and synthetic and/or recombinant biologically active peptide derivatives of parathyroid hormone (e.g., hPTH(1-28)), such as described in U.S. Patent No. 6,417,333 to Bringhurst et al. The PTH may be native or synthesized by chemical or recombinant means.

The PTH may or may not be in lyophilized form, depending upon the desired  
15 formulation and storage requirements. For example, the PTH could be provided in a lyophilized salt form, such as a chloride or acetate (e.g., as hPTH(1-34)Cl or PTH(1-34)OAc), which could be sealed in the reservoirs under nitrogen gas with low water content, without excipient. Alternatively, lyophilized PTH can be suspended in a non-solvent (e.g., non-aqueous) vehicle. In another embodiment, the PTH can be  
20 incorporated into micelles or liposomes.

In one embodiment, the release system comprises PTH dried or lyophilized with an excipient that promotes re-dissolution upon release. Such a composition would accelerate the rate of release (i.e., reduce the pulse duration). An example of a suitable excipient in this embodiment is polyethylene glycol having a molecular  
25 weight between about 100 and 10,000 Daltons.

Excipient

In one embodiment, the release system includes PTH in (e.g., in a mixture with) a pharmaceutically acceptable excipient. As used herein, the term “excipient” is used broadly to include virtually any suitable drug delivery vehicle.

30           The excipient may be a solvent or non-solvent for the PTH to prepare a solution or suspension of the PTH, respectively. The solvent or non-solvent may be aqueous or non-aqueous, so long as the PTH is substantially stable in the solution or suspension during storage in the reservoirs of the drug delivery device and for the useful lifetime of the device.

In one embodiment, the PTH is provided in suspension with a non-aqueous vehicle suitable for stable storage. Preferred pharmaceutically acceptable excipients include non-aqueous vehicles suitable for suspension and stable storage of PTH at 37 °C for several months, preferably a year or more. The non-aqueous vehicle could be an anhydrous, aprotic, hydrophobic, non-polar liquid, with low reactivity to PTH. Representative examples of non-aqueous vehicles include biocompatible perhalohydrocarbons or unsubstituted saturated hydrocarbons. Examples of these include perfluorodecalin, perfluorobutylamine, perfluorotripropylamine, perfluoro-N-methyldecahydroquinidine, perfluoro-octahydro quinolidine, perfluoro-N-cyclohexylpyrilidine, perfluoro-N,N-dimethylcyclohexyl methylamine, perfluoro-dimethyl-adamantane, perfluorotri-methylbicyclo (3.3.1) nonane, bis(perfluorohexyl) ethene, bis(perfluorobutyl) ethene, perfluoro-1-butyl-2-hexyl ethene, tetradecane, methoxyflurane and mineral oil. See, e.g., U.S. Patent No. 6,264,990 to Knepp et al.

In one embodiment, the PTH is provided in a solution. An example of a non-aqueous (anhydrous) solvent that may be suitable is DMSO (dimethyl sulfoxide).

In another embodiment, the release system comprises PTH dried or lyophilized with an excipient that would promote re-dissolution upon release, such as polyethylene glycol having a molecular weight between about 100 and 10,000 Daltons.

Other suitable pharmaceutically acceptable excipients include various carriers approved for parenteral administration, including saline, Ringer's solution, Hank's solution, and solutions of glucose, lactose, dextrose, mannitol, ethanol, glycerol, albumin, and the like. The release system may optionally include stabilizers, antioxidants, antimicrobials, preservatives, buffering agents, surfactants, dessicants, and other additives useful for storing and releasing PTH from the reservoirs *in vivo*.

#### PTH Dosage

The devices can be used to deliver essentially any medically indicated dosage of PTH. In one embodiment, PTH dosages are between 0.5 and 1.0 µg/(kg·day). In one embodiment, the PTH advantageously is released in daily pulsatile doses of between 10 and 300 µg. For example, each reservoir could contain a single dose, e.g., about 20 µg PTH (1-34) or about 100 to 200 µg PTH (1-84) in a suitable formulation. Release dosages can be varied by a number of techniques, for example, by providing different quantities of drug among different reservoirs (some reservoirs contain 20 µg

of PTH, and others contain 10, 15, or 40 µg of PTH) and/or by combining various numbers of reservoirs to form a single dose (e.g., simultaneously opening two reservoirs each containing 10 µg of PTH).

#### Other Drugs

5           While at least two of the reservoirs (and more likely tens to hundreds of reservoirs) will contain PTH, reservoirs may contain release system consisting or comprising other (non-PTH) drugs for release. These additional drugs may be in the same reservoirs as the PTH or in different reservoirs. Representative examples of these other drugs include bone resorption inhibitors, such as bisphosphonates (e.g.,  
10    alendronate, risedronate sodium), estrogen, selective estrogen receptor modulators (e.g., raloxifene HCl), calcitonins, vitamin D analogs, and calcium salts. In an alternative embodiment of the method for administering PTH, the PTH is delivered (e.g., subcutaneously or intravaginally) from the implanted medical device described herein and the other drug, e.g., an anti-resorptive agent, is administered orally using a  
15    conventional oral dosage form. In either approach (other drug administered from implanted device or orally), the PTH and the other drug(s) may be administered sequentially, concurrently, or simultaneously.

          These other drugs, alone or in combination with a pharmaceutically acceptable excipient, may be in pure solid, liquid (e.g., solution or suspension), or gel form, or  
20    mixed with other materials that affect the release rate and/or time. The drugs may be in the form of solid mixtures including amorphous and crystalline mixed powders, monolithic solid mixtures, lyophilized powders, and solid interpenetrating networks. The drugs may, for example, be in the form of liquid mixtures, including solutions, emulsions, colloidal suspensions, and slurries, or in the form of gel mixtures,  
25    including hydrogels.

#### Reservoir Caps

          As used herein, the term "reservoir cap" includes a membrane or other structure suitable for separating the contents of a reservoir from the environment outside of the reservoir. It generally is self-supporting across the reservoir opening,  
30    although caps having additional structures to provide mechanical support to the cap can be fabricated. Selectively removing the reservoir cap or making it permeable will then "expose" the contents of the reservoir to the environment (or selected components thereof) surrounding the reservoir. In preferred embodiments, the

reservoir cap is selectively disintegrated. As used herein, the term "disintegrate" is used broadly to include without limitation degrading, dissolving, rupturing, fracturing or some other form of mechanical failure, as well as a loss of structural integrity due to a chemical reaction (e.g., electrochemical degradation) or phase change (e.g., melting) in response to a change in temperature, unless a specific one of these mechanisms is indicated. In one specific embodiment, the "disintegration" is by an electrochemical activation technique, such as described in U.S. Patent No. 5,797,898. In another specific embodiment, the "disintegration" is by an electro-thermal ablation technique, such as described in U.S. Patent Application No. 10/641,507, filed August 15, 2003.

In active release devices, the reservoir cap generally includes any material that can be disintegrated or permeabilized in response to an applied stimulus, e.g., electric field or current, magnetic field, change in pH, or by thermal, chemical, electrochemical, or mechanical means.

In one embodiment, the reservoir cap is a thin metal film and is impermeable to the surrounding environment (e.g., body fluids or another chloride containing solution). In one variation, a particular electric potential is applied to the metal reservoir cap, which is then oxidized and disintegrated by an electrochemical reaction, to release the drug from the reservoir. Examples of suitable reservoir cap materials include gold, silver, copper, and zinc.

In another variation, the reservoir cap is heated (e.g., using resistive heating) to cause the reservoir cap to melt and be displaced from the reservoir to open it. This latter variation could be used, for example, with reservoir caps formed of a metal or a non-metal material, e.g., a polymer. In yet another variation, the reservoir cap is formed of a polymer or other material that undergoes a temperature-dependent change in permeability such that upon heating to a pre-selected temperature, the reservoir is rendered permeable to the drug and bodily fluids to permit the drug to be released from the reservoir through the reservoir cap.

In still another embodiment, the reservoir cap is formed of a conductive material, such as a metal film, through which an electrical current can be passed to electrothermally ablate it, as described in U.S. Patent Application No. 10/641,507, filed August 15, 2003. Representative examples of suitable reservoir cap materials include gold, copper, aluminum, silver, platinum, titanium, palladium, various alloys (e.g., Au/Si, Au/Ge, Pt-Ir, Ni-Ti, Pt-Si, SS 304, SS 316), and silicon doped with an

impurity to increase electrical conductivity, as known in the art. In one embodiment, the reservoir cap is in the form of a thin metal film. In one embodiment, the reservoir cap is part of a multiple layer structure, for example, the reservoir cap can be made of multiple metal layers, such as a multi-layer/laminate structure of

5 platinum/titanium/platinum. The reservoir cap is operably (i.e. electrically) connected to an electrical input lead and to an electrical output lead, to facilitate flow of an electrical current through the reservoir cap. When an effective amount of an electrical current is applied through the leads and reservoir cap, the temperature of the reservoir cap is locally increased due to resistive heating, and the heat generated within the  
10 reservoir cap increases the temperature sufficiently to cause the reservoir cap to be electrothermally ablated (i.e., ruptured).

In passive release devices, the reservoir cap is formed from a material or mixture of materials that degrade, dissolve, or disintegrate over time, or that do not degrade, dissolve, or disintegrate, but are permeable or become permeable to  
15 molecules or energy. Representative examples of reservoir cap materials include polymeric materials, and non-polymeric materials such as porous forms of metals, semiconductors, and ceramics. Passive semiconductor reservoir cap materials include nanoporous or microporous silicon membranes.

In one embodiment, the release system containing the molecules to be  
20 delivered is covered by a degradable cap material that is nearly impermeable to the molecules. The time of release of the molecules from the reservoir will be limited by the time necessary for the cap material to degrade or dissolve. In another embodiment, the cap material is non-degradable and is permeable to the molecules to be delivered. The physical properties of the material used, its degree of crosslinking,  
25 and its thickness will determine the time necessary for the molecules to diffuse through the cap material. If diffusion out of the release system is limiting, the cap material delays the onset of release. If diffusion through the cap material is limiting, the cap material determines the release rate of the molecules in addition to delaying the onset of release.

30 In one embodiment, a passive, layered release system to provide pulsatile release is used in combination with an actuatable reservoir cap.

Figure 3 illustrates a microchip device for the passive release of parathyroid hormone. It shows device 40 which includes substrate 41 having three reservoirs 42a, 42b, and 42c, which contain, respectively, release system 43a, 43b, and 43c, which

are covered respectively, by bioerodible or biodegradable reservoir caps 44a, 44b, and 44c. In this embodiment, the thickness of the reservoir caps is different for each reservoir cap to provide different times of PTH release.

Any combination of passive and/or active release reservoir cap can be present in a single microchip device. For example, the reservoir cap can be removed by electrothermal ablation to expose a passive release system that only begins its passive release after the reservoir cap has been actively removed. Alternatively, a given substrate can include both passive and active release reservoirs.

#### Controlling Release

The device preferably is provided with a control means to control the time at which the PTH or other drug is released from the device, and into the patient's body. At least for PTH, the control means should provide intermittent release, for example, daily over a period of months (e.g., 2, 6, 10, or preferably 12, months or more). The particular features of the control means depend on the mechanism of reservoir cap activation described herein.

For example, the control means can include the hardware, electrical components, and software needed to control and deliver the electric current from a power source to selected reservoir caps for actuation (i.e., opening). The control means can include an input source, a microprocessor, a timer, a demultiplexer (or multiplexer), and a power source. As used herein, the term "demultiplexer" also refers to multiplexers. The power source provides energy to activate the selected reservoir, i.e. trigger release of drug from the particular reservoir desired for a given dose. For example, the operation of the reservoir opening system can be controlled by an on-board microprocessor (e.g., the microprocessor is within an implantable or insertable device). The microprocessor can be programmed to initiate the disintegration or permeabilization of the reservoir cap in response at a pre-selected time or in response to one or more of signals or measured parameters, including receipt of a signal from another device (for example by remote control or wireless methods) or detection of a particular condition using a sensor such as a biosensor. In another embodiment, a simple state machine is used, as it typically is simpler, smaller, and/or uses less power than a microprocessor. The device can also be activated or powered using wireless means, for example, as described in U.S. 20020072784 A1 to Sheppard et al.

In one embodiment, the device includes a substrate having a two-dimensional

array of reservoirs arranged therein, a release system comprising PTH contained in the reservoirs, anode reservoir caps covering each of the reservoirs, cathodes positioned on the substrate near the anodes, and means for actively controlling disintegration of the reservoir caps. The means includes a power source and circuitry  
5 to control and deliver an electrical potential energy drives a reaction between selected anodes and cathodes. Upon application of a potential between the electrodes, electrons pass from the anode to the cathode through the external circuit causing the anode material (reservoir cap) to oxidize and dissolve into the surrounding fluids, exposing the release system containing the PTH for delivery to the surrounding fluids,  
10 e.g., *in vivo*. The microprocessor directs power to specific electrode pairs through a demultiplexer as directed by a PROM, remote control, or biosensor.

In another embodiment, the activation energy initiates a thermally driven rupturing or permeabilization process, for example, as described in PCT WO 01/12157. For example, the means for controlling release can actively disintegrate or  
15 permeabilize a reservoir cap using a resistive heater. The resistive heater can cause the reservoir cap to undergo a phase change or fracture, for example, as a result of thermal expansion of the reservoir cap or release system, thereby rupturing the reservoir cap and releasing the PTH from the selected reservoir. The application of electric current to the resistor can be delivered and controlled using components as  
20 described above for use in the electrochemical disintegration embodiment. For example, a microprocessor can direct current to select reservoirs at desired intervals.

In yet another embodiment, control means controls electro-resistive ablation of the reservoir cap. For example, the drug delivery device could include a reservoir cap formed of an electrically conductive material, which prevents the PTH from passing  
25 out from the device; an electrical input lead connected to the reservoir cap; an electrical output lead connected to the reservoir cap; and a control means to deliver an effective amount of electrical current through the reservoir cap, via the input lead and output lead, to locally heat and rupture the reservoir cap to release the PTH. In one embodiment, the reservoir cap and conductive leads are formed of the same material,  
30 where the temperature of the reservoir cap increases locally under applied current because the reservoir cap is suspended in a medium that is less thermally conductive than the substrate. Alternatively, the reservoir cap and conductive leads are formed of the same material, and the reservoir cap has a smaller cross-sectional area in the direction of electric current flow, where the increase in current density through the



reservoir cap causes an increase in localized heating. The reservoir cap alternatively can be formed of a material that is different from the material forming the leads, wherein the material forming the reservoir cap has a different electrical resistivity, thermal diffusivity, thermal conductivity, and/or a lower melting temperature than the material forming the leads. Various combinations of these embodiments can be employed.

Microelectronic device packages are typically made of an insulating or dielectric material such as aluminum oxide or silicon nitride. Low cost packages can also be made of plastics or reinforced epoxies (similar to those used in making printed circuit boards). Their purpose is to allow all components of the device to be placed in close proximity and to facilitate the interconnection of components to power sources and to each other, while protecting the electronics from the environment. Implanted microchip device packages will need to be hermetically sealed, e.g., in a titanium encasement, which essentially exposes only the reservoir caps.

The control means can include a microprocessor, a timer, a demultiplexer, and an input source (for example, a memory source, a signal receiver, or a biosensor), and a power source. The timer and demultiplexer circuitry can be designed and incorporated directly onto the surface of the microchip during electrode fabrication, or may be incorporated in a separate microchip. The criteria for selection of a microprocessor are small size, low power requirement, and the ability to translate the output from memory sources, signal receivers, or biosensors into an address for the direction of power through the demultiplexer to a specific reservoir on the microchip device. Selection of a source of input to the microprocessor such as memory sources, signal receivers, or biosensors depends on the microchip device's particular application and whether device operation is preprogrammed, controlled by remote means, or controlled by feedback from its environment (i.e. biofeedback).

A microprocessor is used in conjunction with a source of memory such as erasable programmable read only memory (EPROM), a timer, a demultiplexer, and a power source such as a battery or a biofuel cell. A programmed sequence of events including the time a reservoir is to be opened and the location or address of the reservoir is stored into the EPROM by the user. When the time for exposure or release has been reached as indicated by the timer, the microprocessor sends a signal corresponding to the address (location) of a particular reservoir to the demultiplexer. The demultiplexer routes an input, such as an electric potential or current, to the

reservoir addressed by the microprocessor.

In one embodiment of a passive release embodiment, the means for controllably releasing comprises the release system having different layers of disintegratable materials such that pulsatile release of the parathyroid hormone is provided by disintegration of the layers. For example, a single pulse from each reservoir using multiple reservoirs effectively provides a pulsatile release profile. Alternatively, a pulsatile release profile can be provided from a single reservoir, for example, by incorporating several layers of a release system and other materials into a single reservoir. In either case, the reservoir caps can be formed from a material that degrades or dissolves over time, or does not degrade or dissolve, but is permeable to the PTH molecules to be delivered. These materials are preferably polymeric materials. Materials can be selected for use as reservoir caps to give a variety of degradation rates, dissolution rates, or permeabilities to enable the release of PTH molecules from different reservoirs at different times and, in some cases, different rates. To obtain different release times (amounts of release time delay), caps can be formed of different polymers (e.g., that dissolve at varying rates), the same polymer with different degrees of crosslinking, or a UV polymerizable polymer. In the latter case, varying the exposure of this polymer to UV light results in varying degrees of crosslinking and gives the cap material different diffusion properties or degradation or dissolution rates. Another way to obtain different release times is by using one polymer, but varying the thickness of that polymer. Thicker films of some polymers result in delayed release time. Any combination of polymer, degree of crosslinking, or polymer thickness can be modified to obtain a specific release time or rate.

The layered release system technique described above for use in achieving a pulsatile PTH release profile advantageously and surprisingly has been found to aid in avoiding undesirable phenomena during release (e.g., aggregation, precipitation of PTH). It was found that when trying to release a solution of PTH at a low pH (e.g., pH 3) through a tiny reservoir opening (e.g., a square having 50 micron sides) and into a physiological solution (pH 7), the PTH could precipitate and block the reservoir opening. While not being bound by any theory, it is believed that this phenomena was due to the salts (e.g., MW ~ 60) in the PTH solution diffusing into the physiological solution at a rate that exceeded the rate of diffusion of the PTH (e.g., MW ~ 4000) due, for example, to the molecular weight (MW) dependence of diffusion rate, to such an extent that the pH of the PTH solution increased to a point

exceeding that required to keep the PTH in solution. (For example, at pH 3, the PTH has a solubility of about 100 µg/ml and at pH 7, the PTH has a solubility of about 20 µg/ml.)

By varying the concentration of the PTH to account for the mass diffusion rate differences, precipitation of the PTH can be avoided, e.g., to keep the PTH concentration (and/or pH) at the reservoir opening sufficiently low. It is believed that the same technique could be used to prevent aggregation/precipitation of other proteins or peptides released from a micro-reservoir system. For example, the release system in a reservoir could comprise layers of different drug content and/or excipient which could effect release rates and localized drug concentrations within and adjacent the reservoir during release. In one embodiment, the reservoir release system comprises alternating layers of drug and non-drug materials. Figure 5 illustrates device 50 comprising substrate 52 having reservoirs covered by reservoir caps 54 and containing a release system that consists of PTH-containing layers 56 which are alternated with excipient layers 58. In another embodiment, the layers comprises different concentrations of PTH, in accordance with the varying diffusion distances (and varying cross-sectional areas for reservoirs having tapered walls) in the reservoir. In such layering techniques, a solid fill is needed, for example, where layers comprises a matrix material (e.g., in the form of a sol or gel) having drug dispersed therein. In one embodiment, the matrix material is a water-soluble, inert polymer, such as polyethylene glycol (PEG), which is solid at 37 °C.

#### Sensors

In an optional embodiment, the microchip device includes a sensor or sensing component. For example, the sensor or sensing component can be located in a reservoir or can be attached to the device substrate. The sensor can operably communicate with the device, e.g., through a microprocessor, to control or modify the drug release variables, including dosage amount and frequency, time of release, effective rate of release, selection of drug or drug combination, and the like. The "sensing component" includes a component utilized in measuring or analyzing the presence, absence, or change in a chemical or ionic species, energy, or one or more physical properties (e.g., pH, pressure). Types of sensors include biosensors, chemical sensors, physical sensors, or optical sensors. Further examples of such sensors and sensor components are described in PCT WO 01/64344. The sensor or

sensing component detects (or not) the species or property at the site of *in vivo* implantation (e.g., in a bodily fluid or tissue), and further may relay a signal to the microprocessor used for controlling release from the microchip device, as detailed below. Such a signal could provide feedback on and/or finely control the release of parathyroid hormone.

In one embodiment, the sensor measures plasma calcium levels in the patient and modulates release of PTH or other drugs in response to the measured calcium level, and the amount of parathyroid hormone released from the microchip is dependent on the level of plasma calcium detected by such a sensor. An example of a calcium sensor is described in Van Den Burg, et al., "An ISFET-Based Calcium Sensor Using a Photopolymerized Polysiloxane Membrane," Sensors & Actuators B, vol.4, pp. 235-38 (1991).

The microchip device may also factor in other information in determining the amount and timing of PTH release. For example, bone density and hydroxyproline levels in the urine may be clinical indicators for PTH treatment, and the presence of hyperthyroidism or fluctuation in calcium homeostasis may relate to the increased calcium levels detected. Such information can be transmitted to the microchip device, preferably wirelessly, from other sensors and/or from a physician inputting the information derived, for example, from diagnostic tests performed on the patient.

There are several different options for receiving and analyzing data obtained with devices located in the microchip devices. Active microchip devices may be controlled by local microprocessors or remote control. Biosensor information may provide input to the controller to determine the time and type of activation automatically, with human intervention, or a combination thereof.

Typically, the operation of the microchip system will be controlled by an on-board (i.e. within the package) microprocessor. The output signal from the device, after conditioning by suitable circuitry if needed, will be acquired by the microprocessor. After analysis and processing, the output signal can be stored in a writeable computer memory chip, and/or can be sent (e.g., wirelessly) to a remote location away from the microchip. Power can be supplied to the microchip system locally by a microbattery or remotely by wireless transmission.

In one embodiment, the microchip device includes one or more biosensors (which may be sealed in reservoirs until needed for use) that are capable of detecting and/or measuring signals within the body of a patient. As used herein, the term

“biosensor” includes sensing devices that transduce the chemical potential of an analyte of interest into an electrical signal (e.g., an ion selective field effect transistor or ISFET), as well as electrodes that measure electrical signals directly or indirectly (e.g., by converting a mechanical or thermal energy into an electrical signal). For example, the biosensor may measure intrinsic electrical signals (EKG, EEG, or other neural signals), pressure, temperature, pH, or loads on tissue structures at various *in vivo* locations. The electrical signal from the biosensor can then be measured, for example by a microprocessor/controller, which then can transmit the information to a remote controller, another local controller, or both. For example, the system can be used to relay or record information on the patient’s vital signs or the implant environment, such as drug concentration.

One embodiment of an implantable active-release microchip device for delivery of PTH is illustrated in Figure 1. It shows, in a perspective view, microchip device 10, which includes substrate/reservoir portion 12 in a biocompatible package 14, such as a titanium encasement. The package 14 further includes battery 16 and other device electronics. Figure 1 also shows a close-up, in a perspective and partial cross-sectional view, of a portion of substrate/reservoir portion 12. The close-up illustrates two reservoirs 22a and 22b in substrate 20, which contain release system 26 comprising parathyroid hormone. The reservoirs 22a and 22b are covered by anodic reservoir caps 24a and 24b, respectively, which could be opened by an electrochemical degradation mechanism upon application of an electric potential between a cathode 25 and the anode reservoir caps.

Another embodiment of an implantable active-release microchip device for delivery of PTH is illustrated in Figure 2. As in Figure 1, it shows, in a perspective view, microchip device 10, which includes substrate/reservoir portion 12 in a biocompatible package 14, such as a titanium encasement. The package 14 further includes battery 16 and other device electronics. The close-up view in Figure 2 also shows, in a perspective and partial cross-sectional view, a portion of substrate/reservoir portion 12, illustrating two reservoirs 28 and 32 in substrate 20, which contain release system 26 comprising parathyroid hormone. In this embodiment, the reservoirs 28 and 32 are covered by reservoir caps 28a and 32a, respectively. Reservoir cap 28a is electrically connected to electrical input lead 28b and to electrical output lead 28c, and reservoir cap 32a is electrically connected to electrical input lead 32b and to electrical output lead 32c. These reservoir caps could

be opened via a thermal rupturing mechanism by passing an electric current through the caps in an amount effective to locally heat the cap material and rupture the reservoir cap.

## **II. Methods of Making the Medical Devices**

5           Methods for making the substrate, reservoirs, and reservoir opening/activation components are described for example in U.S. Patent No. 5,797,898; U.S. Patent No. 6,123,861; U.S. Patent Application Publication No. 2002/0107470; U.S. Patent Application Publication No. 2002/0151776, and U.S. Patent Application Publication No. 2002/0183721, as well as U.S. Application No. 10/641,507. In one embodiment,  
10 a MEMS technique is used to make the substrate, reservoirs, and reservoir caps. In another embodiment, standard machining techniques, such as drilling or laser machining are used to make the substrate and reservoirs.

In yet another embodiment, soft lithography, microcontact printing, or the like is used. For example, these techniques can be useful for forming leads and reservoir  
15 caps on non-planar substrates. See, e.g., U.S. Patent No. 6,180,239; No. 5,951,881; No. 6,355,198; and No. 6,518,168.

In one embodiment, the assembly of a complete microchip drug delivery device involves a number of packaging steps, including (1) attachment of electrical leads to the substrate, (2) filling of the reservoirs with a release system comprising  
20 PTH, (3) sealing the reservoirs, (4) integration with electronic components and power sources, and (5) placing the microchip(s) and associated components within a single biocompatible enclosure or "package." The package optionally may be conformally coated with parylene or an inert ceramic material (see e.g., U.S. Patent Application Publication No. 2002/0187260). In some embodiments, insulating or dielectric  
25 materials are deposited over the reservoir cap, leads, or entire surface of the device by methods such as chemical vapor deposition (CVD), electron or ion beam evaporation, sputtering, or spin coating to protect the device or enhance biostability/biocompatibility. Examples of such materials include oxides, nitrides, carbides, diamond or diamond-like materials, or fluorocarbon films. Methods for  
30 assembling, sealing, and packaging microchip chemical delivery devices useful herein are described, for example, in U.S. Patent No. 6,123,861, U.S. Patent Application Publication No. 2002/0119176 and No. 2003/0010808, which are expressly incorporated herein by reference.

In one embodiment, the step of reservoir sealing and the step of formation of a

reservoir cap over the reservoir opening can be combined. This is particularly useful for devices in which the reservoirs are filled and released from the same side, for example, in embodiments where the reservoirs are formed in a substrate without penetrating through the entire thickness of the substrate. In an alternative  
5 embodiment, the reservoir is filled from an opening in the end of the reservoir distal the reservoir cap, and then this opening is permanently sealed.

### III. Uses of the Medical Devices

The microchip devices and release methods described herein can be used to deliver (i.e., administer) parathyroid hormone to a patient for a variety of treatments.  
10 For example, the devices and methods can be used to reduce the incidence of bone fractures, defects, and disorders which result from weakened bones due to as osteoporosis, osteoarthritis, Paget's disease, osteomalacia, bone loss resulting from multiple myeloma and other forms of cancer, bone loss resulting from side effects of other medical treatment (such as steroids), and age-related loss of bone  
15 mass. In addition, the microchip device could be used for strengthening a bone graft, for treating prosthetic ingrowth such as promoting bone ingrowth into a bone prosthesis, for treating a bone fracture, or for treating childhood idiopathic bone loss in a child.

As used herein, the term "patient" refers to a living vertebrate animal such as a  
20 mammal (e.g., human) in need of treatment, i.e., in need of bone repair, augmentation, or replacement. The term "treatment" refers to (1) providing a patient with an amount of a substance sufficient to act prophylactically to prevent the development of a weakened and/or unhealthy state; (2) providing a patient with a sufficient amount of a substance so as to alleviate or eliminate a disease state and/or the symptoms of a  
25 disease state, and a weakened and/or unhealthy state; (3) providing a patient with an amount of a substance sufficient to promote bone formation; or (4) providing combinations of such substances.

In one embodiment, the microchip device is implanted into the patient for long-term delivery of PTH, alone or in combination with other drugs. "Long term"  
30 refers to release over an extended period (e.g., between 1 week and 3 years, between 6 weeks and 2 years, between 3 months and 1 year, etc.). The microchip device can be implanted *in vivo* using standard surgical or minimally invasive implantation techniques, e.g., via a catheter, at any suitable site. Preferred sites include subcutaneous pectoral or abdominal sites. Depending upon the particular

administration route or implantation site, the microchip device can be used for local, regional, or systemic delivery of PTH.

In one embodiment, the medical device is adapted to deliver the PTH by the vaginal route. The medical device could use active release or could rely solely on  
5 passive release to deliver the PTH. A particular advantage of using the vaginal route of administration for delivering PTH is that deployment of the device is not surgical. No implantation procedure is necessary; rather the device is manually inserted into the vagina of the patient, not unlike a tampon or conventional vaginal ring device. In one  
10 embodiment, the device would be designed for more frequent replacement than would be desirable for a subcutaneous device. In such an embodiment, the device would not need to hold as much PTH as the device for subcutaneous implantation. In an active embodiment, the control electronics and power source could also be simplified, thereby reducing the cost of the device. In one embodiment, the microchip device  
15 could be made to be very small and release daily doses of PTH for one or two months, after which time the device could be removed and replaced with a new one. If appropriate, treatment could be halted immediately at any time by simply removing the device.

In one embodiment, the microchip device includes or is combined with a polymeric (e.g., medical grade silicone rubber) body, such as a strip-, rod-, or torus-  
20 shaped device. The body can be, for example, in the form of a vaginal ring-like device (see e.g., U.S. Patent Application Publication No. 20020161352, U.S. Patent No. 4,822,616, and U.S. Patent No. 4,012,496, for description of vaginal rings that can be modified for use herein). A patient or a caregiver can manually place the device into the vagina, where the device remains secured in place by contact (e.g.,  
25 frictional engagement) with the vaginal walls. In one embodiment, the vaginal ring device could include a polymeric coating that is bioadhesive to mucosal surfaces. Preferably no suturing or other more permanent securing means would be required. In one technique, the vaginal ring/microchip device could include an expandable portion that expands upon insertion to enhance the frictional engagement with the  
30 vaginal walls. In another technique, the vaginal ring/microchip device is selected to have a size appropriate for a particular patient.

In yet another embodiment, an array of discrete microreservoirs are fabricated directly into a vaginal ring body (which serves as the substrate), as illustrated in Figures 6-7. The substrate is (integral with) the attachment body. These figures show



device 60 having ring-shaped body 62 in which a plurality of reservoirs containing a PTH formulation 66 are located. The reservoirs are sealed by (generic) reservoir caps 64. The reservoir caps may be opened by any of a number of passive or active techniques described herein. Active control means can be embedded (e.g., within a  
5 compartment) in the ring-shaped body. The body can be a multilayer structure, for example it could have a rigid core portion and a soft polymeric shell.

In a preferred embodiment, the drug-release side of the microchip device is positioned toward and in contact with the mucosal tissues of the vaginal wall. This facilitates transport of the drug from a reservoir, upon opening, to moist vaginal  
10 tissues, enabling the drug to diffuse into the capillaries and other small blood vessels in the tissue, for systemic delivery. Accordingly, in one embodiment of the PTH formulation for vaginal administration, the PTH composition is formulated with a penetration enhancer or absorption promoter to enable such penetration, absorption, transfer or transport through the mucosa.

15 Once the microchip device is placed at the site that PTH delivery (i.e., release) is desired, the PTH can be controllably released from one or more of the reservoirs, either actively or passively, in a pharmaceutically effective amount at the desired dosing schedule. The term "pharmaceutically effective" refers to that amount which effects the formation and differentiation of bone.

20 Generally, each reservoir is loaded with between about 10 and about 300  $\mu\text{g}$  of parathyroid hormone. In a preferred therapy, the microchip device delivers daily doses (pulses) of 20  $\mu\text{g}/\text{day}$  of PTH (1-34) for one year, in order to grow bone, to restore lost bone mass.

The width (i.e., duration) of each pulse dose of PTH is selected to be a  
25 therapeutically effective period. In one embodiment, the duration of each pulse is less than four hours (e.g., less than three hours, less than two hours, less than one hour).

In a typical treatment method, the patient would first receive PTH by injection for the first one or two months of therapy to ensure that the patient experiences no adverse reactions (e.g., hypercalcemia) to the PTH treatment. Once it has been  
30 established that the patient is accepting treatment with adverse reaction, then the microchip device for PTH delivery would be implanted into the patient. The microchip device would then provide administration of PTH, obviating the need for injections going forward. Preferably, a single microchip device provides least all of

the PTH doses required over the course of therapy. For example, the device could contain enough PTH to provide daily doses for between about 10 months and about 12 months.

After the PTH treatment regimen is completed (e.g., after about one year), a treatment with one or more anti-resorptive agents is typically begun. For example, the treatment could include daily doses of a chronic bone loss inhibitor, for up to five years. Optionally, the same device further provides some or all of the doses of anti-resorptive agent. In other methods, the PTH is administered from the implanted microchip device, and the anti-resorptive agent is administered by another route suitable for the selected anti-resorptive agent, such as orally or by parental injection.

In one embodiment, which could be implanted, a single, non-refillable microchip device is provided with at least a year's supply of PTH for delivery. For example, the microchip device could have a substrate provided with a 400-reservoir array, with each reservoir containing a single dose, e.g., about 20  $\mu$ g PTH (1-34) or about 100 to 200  $\mu$ g PTH (1-84) in a suitable formulation.

For example, in an active-release embodiment, the microchip device can be controlled by a pre-programmed microprocessor to open a one or a portion of the reservoirs intermittently (that is, a different one or more reservoirs after each period) to effect release intermittently, e.g., in a pulsatile manner. In other variations, the microprocessor (and thus release) is controlled by a sensor, e.g., a biosensor, or by remote control.

In one embodiment of a passive release microchip device, the PTH can be controllably released using reservoir caps formed of a biodegradable material (e.g., a polymer, such as PLGA). Release times can be controlled and varied by altering the thickness of the reservoir cap, the composition of the reservoir cap (e.g., degree of crosslinking, etc.), or both.

In other embodiments, another drug is released before, simultaneously with, or following one or more releases of PTH. For simultaneous release, the other drug can be contained in the same reservoirs that contain the PTH or the other drug can be contained in one or more separate reservoirs. The other drug can be controllably released in a continuous or intermittent manner. For example, PTH and raloxifene may be administered sequentially, concurrently, or simultaneously as a single composition to the patient. If administered sequentially, the period between the

administration of PTH and raloxifene will typically be one week to one year, and optimally, one week to six months. In a preferred administration scheme, the patient will, after administration of PTH, with or without raloxifene, be administered raloxifene after cessation of administration of PTH.

- 5           In one embodiment, the PTH is released intermittently from the microchip device during a period between 6 and 24 months, and then once PTH administration has been completely, a bone resorption inhibitor is released during a period between about 6 and 36 months.

- Methods of using microchip devices for controlled release of drug and other  
10   molecules is further described in U.S. Patents No. 5,797,898, No. 6,123,861, No. 6,551,838, No. 6,491,666, and No. 6,527,762, and U.S. Patent Application Publications No. 2002/0138067, No. 2002/0072784, No. 2002/0151776, and No. 2002/0107470.

- Publications cited herein and the materials for which they are cited are  
15   specifically incorporated by reference. Modifications and variations of the methods and devices described herein will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

We claim:

1. A method for extended and controlled delivery of parathyroid hormone to a patient in need thereof comprising:  
implanting a medical device into the patient, the medical device comprising a substrate, a plurality of reservoirs in the substrate, a release system contained in each of the reservoirs, wherein the release system comprises parathyroid hormone; and  
controllably releasing a pharmaceutically effective amount of the parathyroid hormone from the reservoirs.
2. The method of claim 1, wherein the step of controllably releasing provides intermittent release of the parathyroid hormone.
3. The method of claim 1 or 2, wherein the parathyroid hormone is released daily in intermittent doses of between about 10 and 300  $\mu\text{g}$ .
4. The method of claim 3, wherein the daily intermittent doses are released over a period of ten months or more.
5. The method of any of claims 1 to 4, wherein the parathyroid hormone is released in a pulsatile manner, each pulse having a duration of less than four hours.
6. The method of any of claims 1 to 5, wherein the pharmaceutically effective amount of the parathyroid hormone, released over a first period of time, is effective to form bone tissue.
7. The method of claim 6, further administering a pharmaceutically effective amount of a bone resorption inhibitor, released over a second period of time, to maintain bone tissue at a level present after the first period of time.
8. The method of claim 7, wherein the bone resorption inhibitor is selected from the group consisting of bisphosphonates, selective estrogen receptor modulators, calcitonins, vitamin D analogs, and calcium salts.
9. The method of claim 6, wherein the bone resorption inhibitor is administered orally.

10. The method of claim 6, wherein the bone resorption inhibitor is released from reservoirs of the medical device.
11. The method of any of claims 1 to 10, wherein the patient is a female and the step of implantation of the medical device comprises inserting the medical device into the vagina of the patient.
12. A implantable device for the extended, controlled delivery of parathyroid hormone to a patient in need thereof comprising:
  - a substrate;
  - a plurality of reservoirs in the substrate;
  - a release system contained in each of the reservoirs, wherein the release system comprises parathyroid hormone; and
  - a control means for selectively releasing a pharmaceutically effective amount of the parathyroid hormone from each of the reservoirs.
13. The device of claim 12, which is able to release a pharmaceutically effective amount of parathyroid hormone once daily over a period of at least six months.
14. The device of claim 12 or 13, further comprising at least one reservoir which contains a second release system comprising a drug other than parathyroid hormone.
15. The device of claim 14, wherein the drug is an anti-resorptive agent.
16. The device of any of claims 12 to 15, wherein each of the reservoirs contains between about 10 and 300  $\mu\text{g}$  of parathyroid hormone for release.
17. The device of any of claims 12 to 16, wherein the plurality of reservoirs comprises 300 or more reservoirs, each containing a release system comprising parathyroid hormone.
18. The device of any of claims 12 to 17, wherein the release system comprises parathyroid hormone in combination with a pharmaceutically acceptable excipient.
19. The device of any of claims 12 to 18, wherein the release system comprises parathyroid hormone suspended in a non-aqueous vehicle.
20. The device of any of claims 12 to 19, wherein the parathyroid hormone is dried or lyophilized with an excipient that promotes re-dissolution upon release.

21. The device of any of claims 18 to 20, wherein the excipient comprises polyethylene glycol having a molecular weight between about 100 and 10,000 Daltons.
22. The device of any of claims 12 to 21, wherein the control means comprises reservoir caps covering the release system of the reservoirs.
23. The device of claim 22, wherein the control means further comprises means for actively disintegrating or permeabilizing the reservoir caps.
24. The device of claim 23, wherein means for actively disintegrating comprises a power source for passing an electric current or potential through the reservoir caps.
25. The device of claim 24, wherein the reservoir caps comprise an electrically conductive material and are electrically connected to an electrical input lead and to an electrical output lead, and the means for actively disintegrating the reservoir cap comprises means for selectively applying an electrical current through the reservoir cap, via the input lead and output lead, in an amount effective to heat the reservoir cap to cause the reservoir cap to disintegrate to permit release of the parathyroid hormone.
26. The device of claim 24, wherein the means for actively disintegrating the reservoir cap comprises a cathode, a microprocessor, a timer, and a demultiplexer, and wherein the reservoir caps each comprise an anode and upon application of an electric potential between the cathode and anode the reservoir cap disintegrates to permit release of the parathyroid hormone.
27. The device of any of claims 12 to 26, further comprising a sensor.
28. The device of claim 27, wherein the sensor measures plasma calcium.
29. The device of any of claims 12 to 28, wherein the control means comprises multiple layers of release system having different compositions.
30. The device of claim 29, wherein a first two or more of the multiple layers comprise the parathyroid hormone dispersed throughout a solid matrix material comprising a water soluble polymer, and a second two or more of the multiple layers comprise the solid matrix material without parathyroid hormone, each of said first two or more layers being stacked alternately with said second two or more layers.

31. The device of claim 29, wherein said multiple layers comprises a first layer having a first concentration of parathyroid hormone therein, and a second layer having a second concentration of parathyroid hormone therein which is greater or less than the concentration in said first layer.
32. The device of any of claims 12 to 31, capable of vaginal administration of the parathyroid hormone.
33. The device of claim 32, wherein the substrate is part of a ring-shaped or rod-shaped body.
34. The device of any of claims 12-33, wherein the control means comprises:  
a electrically conductive reservoir cap covering each reservoir;  
conducting leads to and from each reservoir; and  
a power source and a controller for selectively delivering an electric current through the reservoir cap effective to rupture the reservoir cap and release a pharmaceutically effective amount of the parathyroid hormone from the reservoir.

FIG. 1

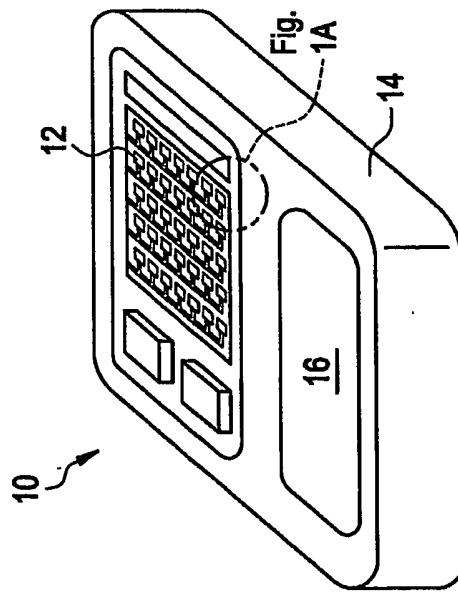


FIG. 1A

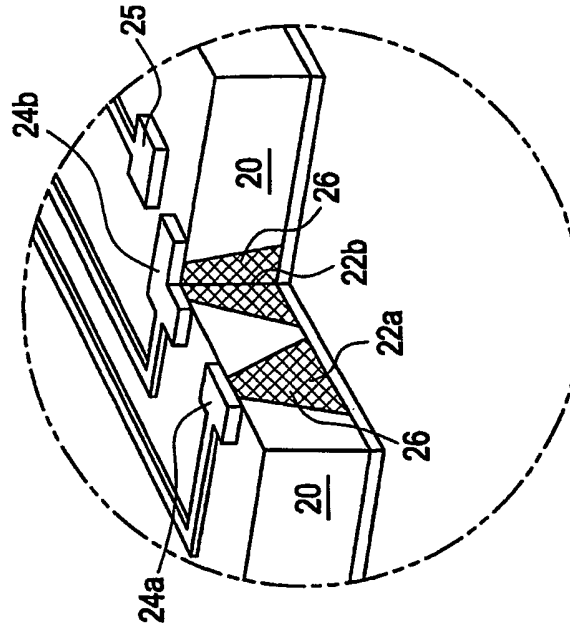




FIG. 2

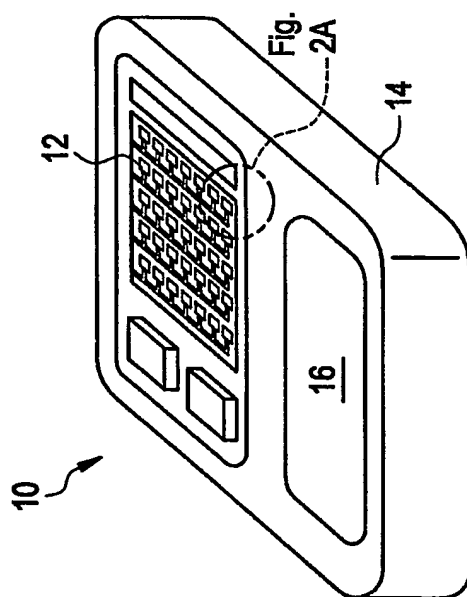


FIG. 2A

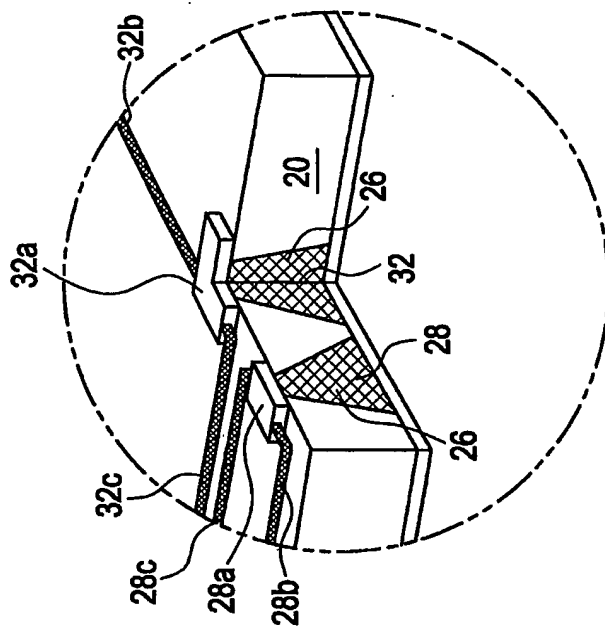


FIG. 3

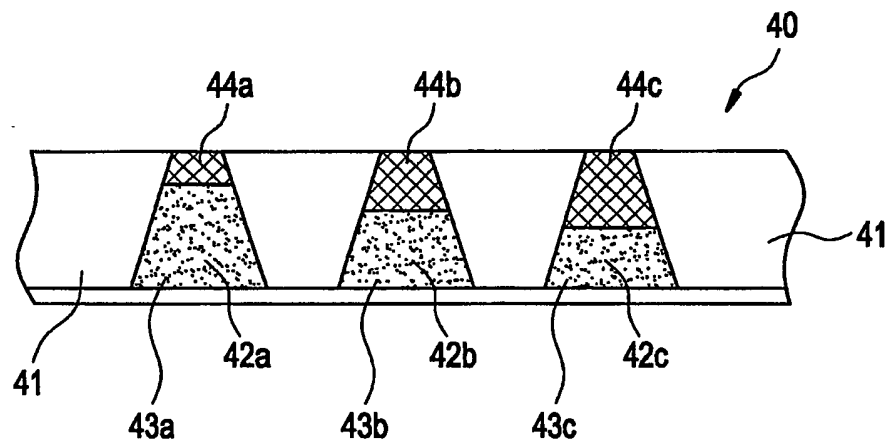


FIG. 4A

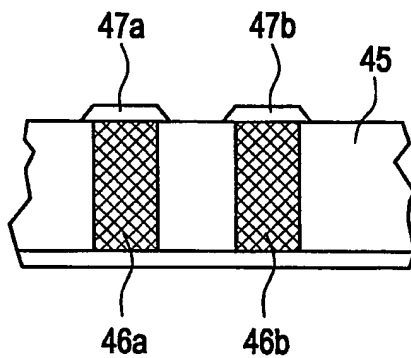


FIG. 4B

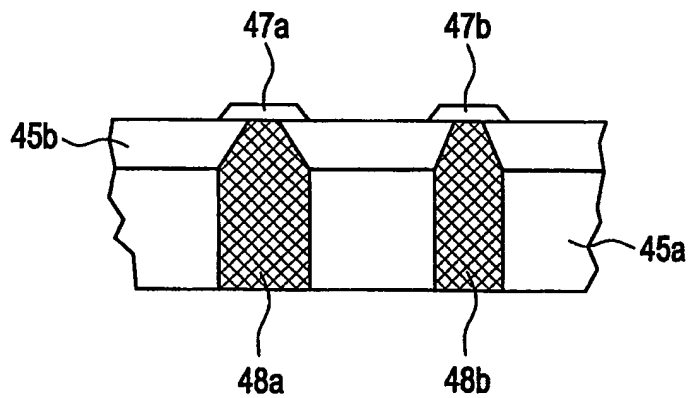


FIG. 5

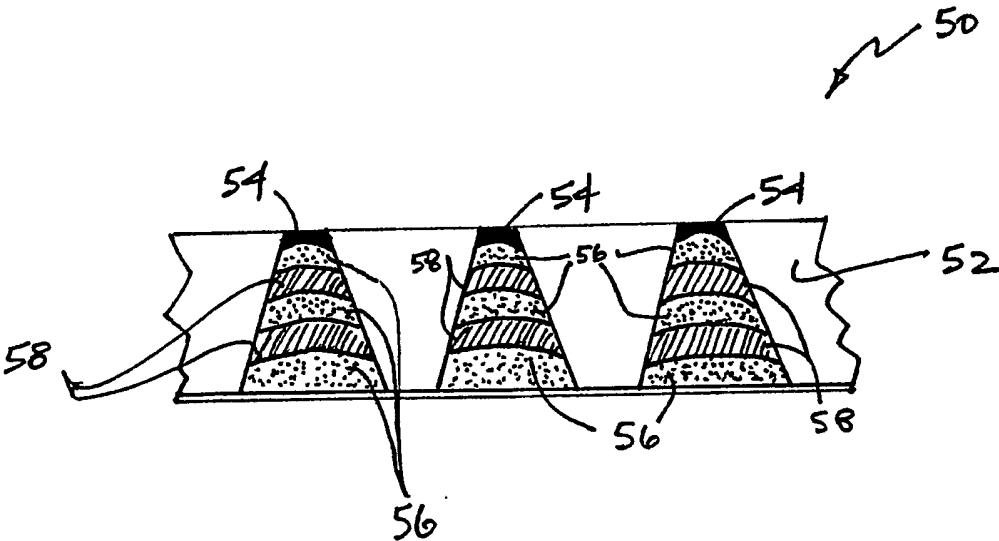


FIG. 6

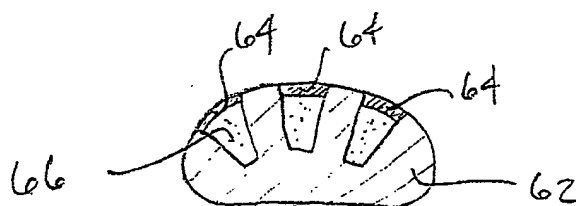
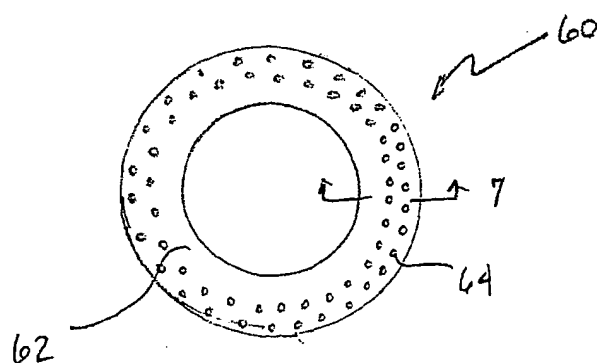


FIG. 7

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/27770

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/00 A61K38/29

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 00107 A (MASSACHUSETTS INST TECHNOLOGY) 8 January 1998 (1998-01-08) cited in the application page 9, line 10 claims 1,25	1-34
P,X	WO 03 032957 A (MICROCHIPS INC) 24 April 2003 (2003-04-24) page 7, line 1 - line 12 page 13, line 1 - line 6	1-34
A	PATENT ABSTRACTS OF JAPAN vol. 017, no. 704 (C-1146), 22 December 1993 (1993-12-22) & JP 05 238929 A (SUMITOMO PHARMACEUT CO LTD; OTHERS: 01), 17 September 1993 (1993-09-17) abstract	1-34
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

11 February 2004

Date of mailing of the international search report

20/02/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hedegaard, A

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/27770

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 306 420 B1 (CHEIKH ROLAND CHERIF) 23 October 2001 (2001-10-23) column 7, line 37 - line 38 claims 1-4 ---	1-34
A	US 2002/107505 A1 (HOLLADAY LESLIE A) 8 August 2002 (2002-08-08) page 6; example 2 claim 1 -----	1-34

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/27770

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy. Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 03/27770

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9800107	A	08-01-1998	US 5797898 A AT 216219 T CA 2258898 A1 DE 69712063 D1 DE 69712063 T2 DK 914092 T3 EP 0914092 A2 ES 2176768 T3 JP 2000513725 T PT 914092 T US 6123861 A WO 9800107 A2	25-08-1998 15-05-2002 08-01-1998 23-05-2002 24-10-2002 12-08-2002 12-05-1999 01-12-2002 17-10-2000 30-09-2002 26-09-2000 08-01-1998
WO 03032957	A	24-04-2003	WO 03032957 A2 US 2003010808 A1	24-04-2003 16-01-2003
JP 05238929	A	17-09-1993	NONE	
US 6306420	B1	23-10-2001	US 6142972 A US 5660846 A US 5837276 A AT 188615 T AT 210424 T AU 3398295 A AU 713066 B2 AU 3398595 A BR 9508687 A CA 2198917 A1 CN 1165479 A DE 69514530 D1 DE 69514530 T2 DE 69524609 D1 DE 69524609 T2 DK 778785 T3 DK 779805 T3 EP 1157703 A2 EP 0778785 A2 EP 0779805 A2 EP 0953362 A2 ES 2141956 T3 ES 2169762 T3 GR 3032947 T3 WO 9607440 A2 WO 9607398 A2 JP 10508294 T LU 91037 A9 PT 778785 T PT 779805 T ZA 9507355 A	07-11-2000 26-08-1997 17-11-1998 15-01-2000 15-12-2001 27-03-1996 25-11-1999 27-03-1996 02-06-1998 14-03-1996 19-11-1997 17-02-2000 27-07-2000 24-01-2002 21-11-2002 29-05-2000 25-02-2002 28-11-2001 18-06-1997 25-06-1997 03-11-1999 01-04-2000 16-07-2002 31-07-2000 14-03-1996 14-03-1996 18-08-1998 22-10-2003 28-04-2000 29-04-2002 25-06-1996
US 2002107505	A1	08-08-2002	AU 6590396 A BE 1009704 A3 BR 9609149 A CA 2220146 A1 DE 19681439 T0 FR 2735132 A1 GB 2317179 A , B IE 960413 A1	24-12-1996 01-07-1997 23-02-1999 12-12-1996 23-07-1998 13-12-1996 18-03-1998 11-12-1996

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/27770

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002107505	A1	IT T0960496 A1	05-12-1997
		JP 11507341 T	29-06-1999
		NL 1003283 C2	02-05-1997
		NL 1003283 A1	09-12-1996
		WO 9639422 A2	12-12-1996
<hr/>			

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ ~~FADED~~ TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**